INTEGRATING RISK PROFILES IN THE TREATMENT CHOICE FOR PATIENTS WITH LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATIC HYPERPLASIA. A SYSTEMATIC ANALYSIS OF EXPERT OPINION

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INTRODUCTION & OBJECTIVES: To explore the potential role of risk factors for disease progression in the treatment choice for patients with lower urinary tract symptoms/benign prostatic hyperplasia (LUTS/BPH).

MATERIAL & METHODS: We used a modified Delphi method to investigate the opinion of 12 international experts on the appropriateness of various treatments for different risk profiles. These risk profiles were unique combinations of clinical variables that predict the risk for disease progression (symptom deterioration, complications, need for invasive treatment). These included age, symptom severity (total I-PSS), prostate volume, prostate specific antigen (PSA), maximum flow rate (Qmax) and post-void residual (PVR). For 324 risk profiles/cases, panellists individually rated the appropriateness of 7 treatments (see table) against a reference therapy ($\alpha 1$-adrenoceptor antagonist continuously: $\alpha 1$-ARc), using a 9-point scale (9=reference treatment is appropriate, 1=alternative treatment is appropriate, 5=equivocal or uncertain). Based on the median score and the extent of agreement, for each of the profiles a panel statement regarding the appropriateness of these treatments was calculated. The relationship between risk factors and panel statements was examined using logistic regression analysis.

RESULTS: Overall, α_1-ARc was considered appropriate in 51% of the cases versus 7% for the alternative treatments. For 42% of the cases, the panel ratings were uncertain. For the majority of cases, treatment with α_1-ARc was considered far more appropriate than watchful waiting (WW), plants and α_1-AR short-term therapy (defined as "until symptoms resolve"). For the appropriateness of α_1-ARc vs. other treatments, the ratings were largely uncertain. Logistic regression analysis showed that a large prostate volume and considerable PVR were the dominant factors in favour of combination therapy and surgery.

Panel judgements (%) on appropriateness of 7 treatments (left column) vs. α_1-ARc (right column)

Treatment:	Appropriateness of treatment (%)		
	Left treatment	Uncertain	α_1-ARc
WW	7	15	78
5α-reductase inhibitor	-	74	26
Plant short-term	-	20	80
Plant continuously	-	16	74
Combination*	19	69	12
Surgery	20	63	17
α_1-AR short-term	-	27	73
Total	7	42	51

Sum of row totals: 100%; * α_1-ARc + 5α-reductase inhibitor

CONCLUSIONS: Although many ratings were uncertain, α_1-AR continuously was considered far more appropriate for treating LUTS/BPH than watchful waiting, plant extracts, and short-term α_1-AR therapy. The choice for combination therapy or surgery over α_1-AR continuously was mainly determined by a large prostate volume and a considerable PVR.

IMMUNOHISTOCHEMICAL PRESENCE OF CYCLIC AMP AND CYCLIC GMP-DEPENDENT PROTEIN KINASE A AND G IN HUMAN CAVERNOUS ARTERIES AND CORPUS CAVERNOSUM

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INTRODUCTION & OBJECTIVES: Although the nitric oxide (NO) - cGMP pathway has been shown to be an important mediator of penile erection, there is evidence that cAMP-dependent mechanisms are also involved in cavernous smooth muscle relaxation. To date, only very few studies have focused on the cAMP- mediated signal transduction in human penile erectile tissue. To further elucidate the role of the cAMP pathway in the control of the human corpus cavernosum and penile vessels, we investigated the occurrence of cAMP- and cGMP-dependent protein kinase A (isoforms 1A and 1B) and G in cavernous tissue and penile arteries.

MATERIAL & METHODS: Human penile erectile tissue (cavernous arteries and corpus cavernosum) was obtained from 6 patients, who underwent male-to-female gender reassignment surgery. Cryostat sections prepared from formaldehyde-fixated tissue segments were incubated with primary antibodies directed against the isoforms 1A and 1B of protein kinase A and against protein kinase G. Then sections were exposed to fluoresce in isothiocyanate (FITC)-labelled secondary antibodies. Visualization was commenced by means of laser microscopy.

RESULTS: FITC-immunostaining indicating the presence of protein kinase A1A and G was abundantly observed within the layer of smooth muscle cells of the media of human cavernous arteries and within trabecular smooth muscle cells of corpus cavernosum. There was fluorescence concerning protein kinase A1A in the endothelial cells of the arterial wall as well. In contrast, protein kinase A1B could not be detected in the arterial wall of cavernous arteries or penile erectile tissue.

CONCLUSIONS: Our results support the significance of the cAMP-dependent pathway in penile erection by the presence of cAMP-dependent protein kinase A not only in cavernous erectile tissue but also within the wall of human cavernous arteries. Furthermore the coexpression of cAMP and cGMP- dependent protein kinase A and G are in accordance with the hypothesis of synergistic activation of protein kinase A and G in penile erection.

IMMUNOHISTOCHEMICAL PRESENCE OF CYLIC ADENOSIN MONOPHOSPHATE AND CYCLIC GUANOSINE MONOPHOSPHATE PHOSPHODIESTERASE ISOENZYMES IN THE HUMAN VAGINA

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INTRODUCTION & OBJECTIVES: Contrary to intensive scientific affords with regard to the physiology and pathophysiology of the male penile erection, the physiology of the female sexuality has only received minimal recognition. As a result, our knowledge regarding the physiology of female sexual response is only sparse. It is well known that with sexual stimulation the luminal diameter of the vagina as well as vaginal lubrication increases. Nevertheless, to date, only very little is known as to the significance of cAMP- and cGMP (cNMP)-mediated signal transduction in the control of the normal function of this process. Thus, it was the aim of our study to elucidate the presence of some cNMP-degrading phosphodiesterases (PDE's) (isoenzymes 3, 4, 5 and 10) in the human vagina by means of immunohistochemical methods.

MATERIAL & METHODS: Cryostat sections prepared from formaldehyde-fixated vaginal wall segments were incubated for 48h with primary antibodies (Dilution 1:250) directed against PDE isoenzymes 3, 4, 5 and 10. Then, sections were incubated with either fluorescein isothiocyanate- (FITC) or Texas Red- (TR) labelled secondary antibodies for 2 h. Visualization was commenced by means of a immunofluorescence.

RESULTS: Immunostaining indicating the presence of PDE4 (cAMP-PDE), 5 (cGMP-PDE) and 10 (cAMP/cGMP-PDE, Dual Substrate PDE) was abundantly observed in the vaginal smooth muscle and arterial vessels. In addition, staining for PDE4 and 10 was also seen in the vaginal epithelium. Although immunoreactivity for PDE3 (cGMP-inhibited PDE) was detected in the epithelial layer, this staining was of inferior degree when compared to the reaction indicating the expression of PDE4 and 10. Neuronal structures in the tissue appeared unstained for all PDE isoenzymes.

CONCLUSIONS: Our results, for the first time, demonstrate the presence of cAMP- and cGMP-PDE's in the human vagina and may indicate a possible regulatory function of these enzymes in the cNMP-mediated control of smooth muscle tone, local blood flow and lubrication. These findings might be of significance with regard to the pharmacological treatment of disorders connected with female sexual arousal and the ability to achieve orgasm, e.g. reduced vaginal lubrication or sensitivity.

ANDROGEN AND ESTROGEN RECEPTORS IN THE HUMAN CORPUS CAVERNOSUM PENIS: IMMUNOHISTOCHEMICAL AND CELL CULTURE RESULTS

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INTRODUCTION & OBJECTIVES: A high quantity of androgen receptors has been documented in fetal and prepubertal penile tissue, but only few studies evaluated sex hormone receptor distribution in adult human tissue of the corpus cavernosum penis. In contrast to several well known central and peripheral nervous effects of androgens the local effect in the penile end organ tissue is still unclear.

MATERIAL & METHODS: Corpus cavernosum biopsies of adult potent patients aged 19 to 63 years undergoing penile deviation surgery (group A; n=8; mean age 37.5 years) and male-to-female transsexual surgery (group B; n=12; mean age=36.9 years) were fixed in formalin and immunostained for nuclear androgen receptor and estrogen-alpha receptor. The percentage of positively stained nuclei in stromal and endothelial cells within the tissue was counted by digitalized high power field imagination.
Additionally, primary corpus cavernosum endothelial cell cultures were obtained by enzymatic isolation from the same groups of patients (n=6). 2x10^4 cells/well seeded in 12-well plates were exposed to testosterone, dihydrotestosterone, estradiol and progesterone likewise (10^{-6}M to 10^{-10}M) for 7 days. At the end of this period cell metabolic activity was measured by the tetrazolium salt-based (MTS) assay and total cell count was performed.

RESULTS: Androgen and estrogen-alpha receptors were detected in stromal as well as in endothelial cells. 74.9% (SD 16.4) of all cell nuclei in group A and 63.5% (SD 17.1) in group B were positively stained for androgen receptors; the respective percentage of estrogen receptors was 11% (SD 9.5) and 21.2% (SD 12.6). Only the increased percentage of positive estrogen receptors in group B, i.e. transsexual patients treated with female sex hormones, compared to group A was significant (t-test; p<0.05).The distribution and amount of androgen and estrogen-alpha receptors was not influenced by the age of the patients. After 7 days of hormone exposure the endothelial cell cultures showed an up to 5-fold increase of total cell count. This cell count correlated to the respective metabolic activity in the MTS test.
Only the cell cultures exposed to testosterone and dihydrotestosterone showed a significant dose-dependent increase of cell metabolic activity and proliferation rate over the two control groups exposed to growth medium with or without ethanol (t-test; p<0.05). On the other hand estradiol and progesterone at same concentrations as androgens had no respective effect in this cell culture system.

CONCLUSIONS: The age-independent high androgen and low estrogen-alpha receptor distribution found in the immunohistochemistry of this study suggests a possible peripheral effect of androgens rather then estrogens at the level of the corpus cavernosum penis. This is supported by the observed effect of testosterone and dihydrotestosterone on endothelial cell metabolism and proliferation in the cell culture system.